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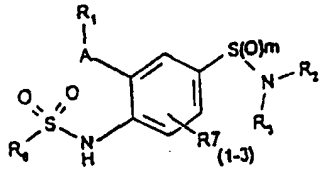
(54) Title: SUBSTITUTED DERIVATIVES OF BENZOSULPHONAMIDES AS INHIBITORS OF THE ENZYME CYCLOOXYGENASE II

(57) Abstract

The present application relates to compounds of formula (I) wherein A represents oxygen, sulfur or –NH–, m is 0–2, and R_1, R_2, R_3, R_6 and R_7 have the meanings given in the specification, to a process for their preparation, as well as to their use in the inhibition of cyclooxygenase II.



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SUBSTITUTED DERIVATIVES OF BENZOSULPHONAMIDES AS INHIBITORS OF THE ENZYME CYCLOOXYGENASE II

The invention relates to novel compounds having anti-inflammatory activity.

Prostaglandins play a decisive role in inflammatory processes and inhibition of the formation of prostaglandin, especially the formation of PGG_2, PGH_2 and PGE_2, is the common characteristic of compounds with anti-inflammatory activity. The known non-steroidal anti-inflammatory drugs (NSAIDs), which reduce prostaglandin-induced pain and swelling during the inflammation process, also influence prostaglandin-regulated processes which do not accompany inflammation processes. For this reason, most known NSAIDs cause undesirable side-effects in high doses, often even dangerous ulcers, especially stomach ulcers, gastric haemorrhages and such like. For this reason, the therapeutic potential of these compounds is decisively reduced.

Most known NSAIDs prevent the formation of prostaglandins by the inhibition of enzymes in human arachidonic acid metabolism, especially by inhibiting the enzyme cyclooxygenase (COX). The enzyme cyclo-oxygenase II (COX-2) is an enzyme of human arachidonic acid metabolism which has only been discovered recently. (Proc. Natl. Acad. Sci. USA, 89, 7384, 1992). COX-2 is induced by cytokines or endotoxins.

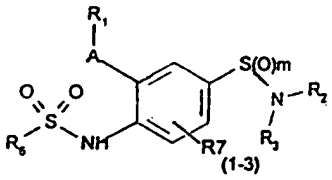
The discovery of this inducible enzyme, which plays a decisive role in inflammation processes, offers the possibility of searching for selectively effective compounds with an anti-inflammatory activity, which inhibit the inflammation process in a more effective manner without influencing other prostaglandin-regulated processes, and thus having fewer and fewer serious side-effects.

5-methylsulphonamide-1-indanones, which inhibit the enzyme cyclooxygenase II and which can therefore be utilised during the treatment of inflammation processes, are known from WO 94/13635. The potential of these compounds, and their side-effects, have not yet been fully clarified. Furthermore, these known compounds dissolve poorly, and thus have decisive disadvantages with regard to their formulation and application. Hence there is still a demand for new cyclooxygenase II-selective compounds, which, due to their effect and side-effect profiles, are safe and efficient in applications for the treatment of inflammatory processes.

The objective of the present invention was thus the provision of new non-steroidal anti-inflammatory drugs (NSAIDs), which selectively inhibit cyclooxygenase II (COX-2) and thus have fewer and fewer serious undesired side effects.

This objective could be unexpectedly solved by the provision of new derivatives of benzenesulphonic acid. As a result of their selective effect on the enzyme Cyclooxygenase II, these new compounds have excellent anti-inflammatory, analgesic, antipyretic and anti-allergic effects, but without the extremely undesirable side-effects of known anti-inflammatory agents.

The subject matter of the invention are thus compounds of formula I



wherein

A denotes oxygen, sulphur or NH,
R_1 is an optionally unsaturated alkyl or alkyloxyalkyl group, optionally mono- or polysubstituted or mixed substituted by halogen, alkoxy, oxo or cyano, a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted or mixed substituted by halogen, alkyl, CF_3, cyano or alkoxy,
R_2 and R_3, independently from one another, denote hydrogen, an optionally polyfluorised alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n$-X,

or

R_2 and R_3, together with the N- atom denotes a 3 to 7-membered, saturated, partially or completely unsaturated heterocycle with one or more heteroatoms N, O or S, which can optionally be substituted by oxo, an alkyl, alkylaryl or aryl group, or a group $(CH_2)_n$-X,

X denotes halogen, NO_2, $-OR_4$, $-COR_4$, $-CO_2R_4$, $-OCO_2R_4$, $-CN$, $-CONR_4OR_5$, $-CONR_4R_5$, $-SR_4$, $-S(O)R_4$, $-S(O)_2R_4$, $-NR_4R_5$, $-NHC(O)R_4$, $-NHS(O)_2R_4$,
n denotes a whole number from 0 to 6,
R_6 denotes a straight-chained or branched alkyl group with 1-10 C- atoms, a cycloalkyl group, an alkylcarboxyl group, an aryl group, aralkyl group, a heteroaryl or

heteroaralkyl group which can optionally be mono- or polysubstituted or mixed substituted by halogen or alkoxy,

R_7 denotes halogen, hydroxy, a straight-chained or branched alkyl, alkoxy, acyloxy or alkyloxycarbonyl group with 1-6 C- atoms, which can optionally be mono- or polysubstituted by halogen, NO_2, $-OR_4$, $-COR_4$, $-CO_2R_4$, $-OCO_2R_4$, $-CN$, $-CONR_4OR_5$, $-CONR_4R_5$, $-SR_4$, $-S(O)R_4$, $-S(O)_2R_4$, $-NR_4R_5$, $-NHC(O)R_4$, $-NHS(O)_2R_4$, or a polyfluoroalkyl group,

R_4 and R_5, independently from one another, denote hydrogen, alkyl, aralkyl or aryl, and

m denotes a whole number from 0 to 2,

and the pharmaceutically-acceptable salts thereof.

A denotes oxygen, sulphur or NH.

R_1 denotes an optionally unsaturated alkyl or alkyloxyalkyl group, each with 1-12 C-atoms in the alkyl chain, for example a methyl, an ethyl, a propyl, an isopropyl, a butyl, an isobutyl, a tertiary-butyl, a pentyl, an isopentyl, a hexyl or an isohexyl group and the like, or for example unsaturated alkyl groups such as ethenyl, butenyl, or alkyoxyalkyl groups such as methoxymethyl, ethoxymethyl and the like. These groups can optionally be substituted by halogen, for example F, Cl or Br, by alkoxy, oxo or cyano. Furthermore, R_1 can denote a cycloalkyl group, for example a cyclohexyl or a cyclopentyl group, an aryl group, for example a phenyl group, or heteroaryl group, for example a furyl, thienyl, thiazolyl, imidazolyl, thiadiazolyl, pyridyl, pyridinyl or pyrazolyl group. These groups can optionally be mono- or polysubstituted or mixed substituted by halogen, for example Cl, F, Br or by CF_3 or alkyl with 1-4 C-atoms, for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl or tertiary-butyl or alkoxy with 1-4 C-atoms, for example methoxy, ethoxy, propoxy or butoxy or cyano.

R_2 and R_3, independently from one another, denote hydrogen, an optionally polyfluorized alkyl group with 1-6 C-atoms, for example methyl, an ethyl, a propyl, an isopropyl, a butyl, an isobutyl, a tertiary-butyl, a pentyl, an isopentyl, a hexyl or an isohexyl group, a CF_3 group or C_2F_5, an aralkyl group with 1-4 C-atoms in the alkyl chain, for example a benzyl group, an ethylphenyl group, an aryl group, for example a phenyl group or a heteroaryl group, for example a pyridyl group, a pyridazinyl group, a thienyl group, a thiazolyl group or an isothiazolyl group.

R_2 and R_3 can also, independently from one another, denote a group $-(CH_2)_n-X$, whereby X is halogen, $-NO_2$, $-OR_4$, $-COR_4$, $-CO_2R_4$, $-OCO_2R_4$, $-CN$, $-CONR_4OR_5$, $-CONR_4R_5$, $-SR_4$, $-S(O)R_4$, $-S(O)_2R_4$, $-NR_4R_5$, $-NHC(O)R_4$, $-NHS(O)_2R_4$, and n is a whole number from 0 to 6.

Examples of such groups are halogen alkyl groups, for example chloromethyl, chloroethyl, the group -CN, nitroalkyl groups, for example nitromethyl, nitroethyl or cyanoalkyl groups, for example cyanomethyl, cyanopropyl, cyanohexyl, a hydroxy group or hydroxyalkyl groups, for example hydroxymethyl, hydroxyethyl, hydroxypropyl bishydroxymethyl-methyl. Other examples are alkoxy groups such as methoxy, ethoxy, propoxy, butoxy, pentoxy, the groups methyloxy-ethyl, ethyloxy-methyl, carboxylic acid groups such as ethoxycarbonyl, methoxycarbonyl, acetyl, propionyl, butyryl, isobutyryl groups and their alkyl-, aralkyl- or aryl esters, carbamoyl groups, oxycarbonyloxy groups, for example the ethoxycarbonyloxy group, carboxymide acid groups, thiocarboxy groups and such like.

R_4 and R_5 denote, independently of one another, hydrogen, alkyl with 1-6 C-atoms, aralkyl with 1-4 C-atoms in the alkyl chain, for example benzyl, ethylphenyl or aryl,

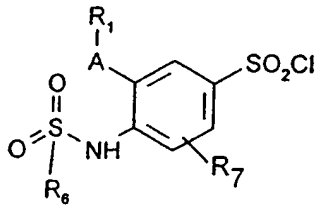
for example phenyl.

Furthermore, R_2 and R_3, together with the N-atom, can form a 3- to 7-membered, saturated, partially or completely unsaturated heterocycle with one or more heteroatoms N, O or S, which may optionally be substituted by oxo, an alkyl, alkylaryl or aryl group or a group $-(CH_2)_n-X$, whereby X denotes halogen, NO_2, $-OR_4$, $-COR_4$, $-CO_2R_4$, $-OCO_2R_4$, $-CN$, $-CONR_4OR_5$, $-CONR_4R_5$, $-SR_4$, $-S(O)R_4$, $-S(O)_2R_4$, $-NR_4R_5$, $-NHC(O)R_4$, $-NHS(O)_2R_4$, and n is a whole number from 0 to 6.

Examples of such rings are the morpholyl group, the aziridinyl group, the azetidinyl group, the pyridyl group, the pyrazolyl group, the thiazolyl group and such like.

R_6 denotes a straight chain or branched alkyl group with 1-10 C-atoms, for example methyl, an ethyl, a propyl, an isopropyl, a butyl, an isobutyl, a tertiary-butyl, a pentyl, an isopentyl, a hexyl or an isohexyl group or such like, a CF_3 group or C_2F_5, an aralkyl group with 1-4 C-atoms in the alkyl chain, for example a benzyl group, an ethylphenyl group, an aryl group, for example a phenyl group or a heteroaryl group, for example a pyridyl group, a pyridazinyl group, a thienyl group, a thiazolyl group or an isothiazolyl group or a heteroaralkyl group, for example. These groups can, for example, be mono- or polysubstituted or mixed substituted by halogen, for example Cl, F or Br, or alkoxy, for example methoxy, ethoxy and such like, by $-NO_2$, $-OR_4$, $-COR_4$, $-CO_2R_4$, $-OCO_2R_4$, $-CN$, $-CONR_4OR_5$, $-CONR_4R_5$, $-SR_4$, $-S(O)R_4$, $-S(O)_2R_4$, $-NR_4R_5$, $-NHC(O)R_4$, $-NHS(O)_2R_4$.

The compounds, according to the invention, can be prepared by reacting a compound of formula III



III

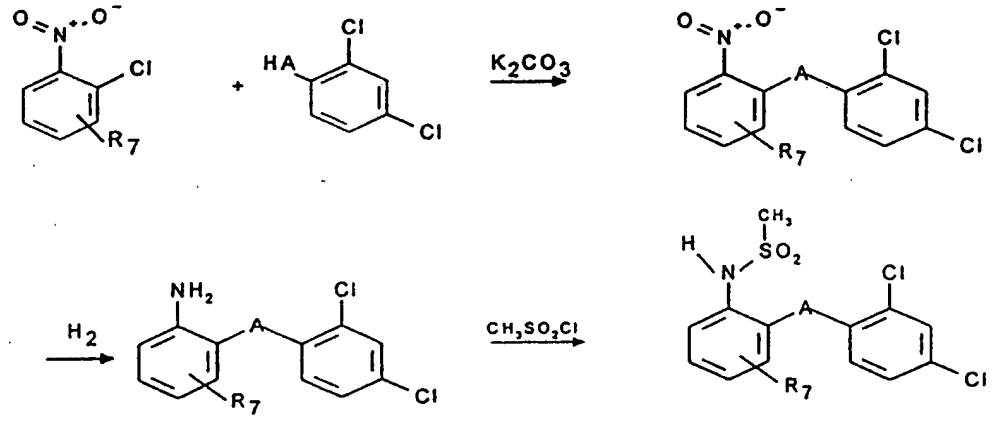
with a compound of formula IV

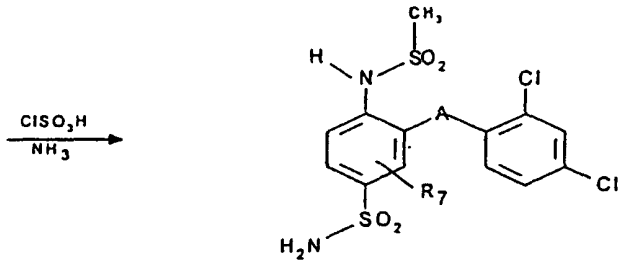
HNR_2R_3 IV

or a salt thereof.

This reaction preferably takes place in the presence of a diluent or solvent which is inert under reaction conditions, for example dioxan, tetrahydrofuran or such like. The reaction temperature is approximately -10°C up to the reflux temperature of the solvent or diluent preferably -10°C up to room temperature.

The starting compounds of formula III can, for example, be prepared according to the following reaction scheme or by other methods familiar to the skilled person.





The compounds of formula I, obtained as described above, are acidic or basic compounds and can be converted in the usual manner with inorganic or organic bases or acids respectively into their pharmaceutically-acceptable salts. The salt formation can, for example, be carried out by adding at least an equivalent quantity of the desired base or acid to a compound of formula I in a suitable solvent, such as for example water, acetone, acetonitrile, benzene, dimethylformamide, dimethyl-sulphoxide, chloroform, dioxan, methanol, ethanol, hexanol, ethylacetate, or in an aliphatic ether, for example diethylether, or mixtures of such solvents, being mixed well, and after completion of salt formation the precipitated salt is filtered off, lyophilised or the solvent is distilled off in a vacuum. If necessary, the salts can be recrystallised after isolation.

Pharmaceutically-acceptable salts are those with inorganic acids, such as for example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid or nitric acid, or with organic acids such as citric acid, tartaric acid, maleic acid, fumaric acid, succinic acid, malic acid, methanesulphonic acid, aminosulphonic acid, acetic acid, benzoic acid and such like.

Pharmaceutically-acceptable salts are e.g. metallic salts, especially alkaline metal or alkaline-earth metal salts such as sodium, potassium, magnesium or calcium salts. Other pharmaceutical salts are, for example, easily-crystallising ammonium salts. These are derived from ammonia or organic amines, such as mono-, di- or tri-lower-(alkyl, cycloalkyl or hydroxyalkyl)-amines, lower alkylene diamines or hydroxy- or aryl-lower-alkyl ammonium bases e.g. methylamine, diethylamine, triethylamine, ethylenediamine, tris-(hydroxymethyl)-aminomethane, benzyltrimethylammonium hydroxide and such like.

The new compounds have good solubility and, as a result of their selective effect on the enzyme cyclooxygenase II, they have excellent anti-inflammatory, analgesic, antipyretic and antiallergic effects, but without the extremely undesirable side-effects of known anti-inflammatory agents.

As a result of this pharmacological characteristic, the new compounds can be used, individually or in combination with other effective substances in the form of common galenic preparations as medicaments for the treatment of disorders or diseases which can be treated or healed by inhibition of the enzyme cyclooxygenase II.

These disorders or diseases embrace pain, fever and inflammations of various types, for example rheumatic fever, symptoms associated with influenza or other viral infections, head and joint pains, toothache, sprains, distortions, neuralgia, muscle inflammation, joint inflammation, joint membrane inflammation, arthritis, rheumatoid arthritis, other rheumatic inflammation form degenerative manifestations, for example osteoarthritis, gouty arthritis, stiffening of the joints, spondylitis,

bursitis, burns and injuries.

The invention thus relates to pharmaceutical preparations which contain the compounds of formula I, according to the invention, or their salts, alone or mixed with other therapeutically-active substances, as well as common galenic adjuvant and/or carrier substances or diluents.

The compounds according to the invention can be orally applied in the form of tablets or capsules which contain a single dose of the compound together with adjuvant substances and diluents such as maize starch, calcium carbonate, dicalcium phosphate, algenic acid, lactose, magnesium stearate, primogel or talcum. The tablets are manufactured in the traditional manner by granulating the contents and pressing into shape, the capsules by filling hard gelatine capsules of suitable size.

A further application form of the compounds, according to the invention, are suppositories which contain adjuvant substances such as beeswax derivatives, polyethylene glycol or polyethylene glycol derivatives, linoleic acid or linoleic acid esters, together with a single dose of the compound and which are rectally administered.

The compounds, according to the invention, can also be parenterally applied, for example by intramuscular, intravenous or subcutaneous injection. For parenteral application, it is best that they are used in the form of a sterile aqueous solution, which can contain other dissolved materials such as tonic agents, agents for standardization of the pH value, preservatives and stabilisers. Distilled water can be added to the compounds and the pH value can be adjusted to between 3 and 6 by using, for example, citric acid, lactic acid or

hydrochloric acid. Sufficiently-dissolved materials, such as dextrose or salt solutions, can be added in order to isotonically set the solution. In addition, preservatives such as p-hydroxybenzoate, and stabilisers such as EDTA, can be added to give the solution a sufficient shelf-life and stability. The solution obtained in this way can then be sterilised and decanted into sterile ampoules of a suitable size so that they contain the desired volume of solution. The compounds, according to the invention, can also be applied by infusion of a parenteral formulation as described above.

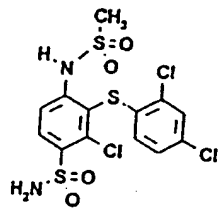
Furthermore, the compounds, according to the invention, can be formulated for topical or transdermal application with suitable adjuvant and/or carrier substances, emulsifiers, tensides and/or diluents, e.g. vaseline, olive oil, peanut oil, sesame seed oil, soya oil, water, glycols, cetylstearyl esters, triglycerides, cetaceum, miglyol and such like into ointments, creams, gels or plasters, or for example formulated into powder with talcum.

For oral application with humans, it is accepted that the daily dosage of a compound according to the invention, will lie in the range of 0.01 to 1000 mg per day for a typical adult patient of 70 kg. Hence tablets or capsules can usually contain 0.003 to 300 mg of active compound, for example 0.1 to 50 mg, for oral application up to three times per day. With parenteral administration, the dose can lie in the range of 0.001 to 1000 mg per 70 kg per day, for example approximately 5 mg.

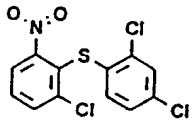
Example 1: 3-(2,4-Dichlorophenylthio)-2-chloro-4-methylsulphonylamino-benzosulphonamide

$C_{13}H_{11}Cl_3N_2O_4S_3$

FW: 461.79 $gmol^{-1}$

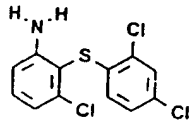


a) 3-chloro-2-(2,4-dichlorophenylthio)-nitrobenzene



Sodium carbonate (13.8g) is added to a solution of 1,2-dichloro-3-nitrobenzene (19.2g) and 2,4-dichlorothiophenol (17.9g) in xylene (250 ml), and the resulting mixture is heated for 5 hours at reflux temperature. The precipitate is separated by filtration, washed with xylene and the combined organic phases are concentrated. The resultant residue is mixed with petroleum ether and stirred for 1 hour at room temperature. Following this, the crystalline material is suction filtered and washed with petroleum ether, and any remaining solvent is removed in a vacuum. Yield: 25.6g of colourless crystals (76.6%).

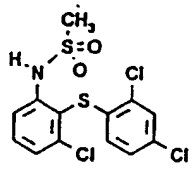
b) 3-chloro-2-(2,4-dichlorophenylthio)-aniline



A solution of 3-chloro-2-(2,4-dichlorophenylthio)-nitrobenzene (10.04g) in dioxan (100 ml) is mixed with Raney-nickel (5g). Following this, the mixture is shaken for 3 hours at room temperature and 3 bar hydrogen pressure in a Parr apparatus. The catalyst is removed by filtration. The filtrate is concentrated in a vacuum and the resulting residue is brought to constant weight in a vacuum. Yield 9.01g (98.6%) of colourless oil.

^{13}C-NMR ($CDCl_3$, 100 MHz): δ 151.1, 141.4, 133.4, 131.9, 131.8, 131.3, 129.3, 127.5, 126.6, 119.4, 113.5, 111.2.

c) 3-chloro-2-(2,4-dichlorophenylthio)-N-methyl-sulphonyl-aniline

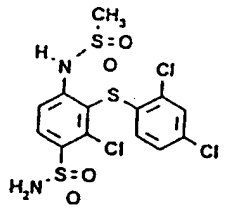


3-chloro-2-(2,4-dichlorophenylthio)-aniline (8.96g) is dissolved in pyridine (300 ml). Methane sulphochloride (4.56 ml) is added dropwise to this solution and the resulting mixture is stirred for 12 hours at room temperature. Following this, the mixture is emptied onto iced water, acidified with concentrated hydrochloric acid. The resulting mixture is extracted 3 times with methylene chloride (each 200 ml). The combined organic phases are dried (Na_2SO_4), filtered and the filtrate is concentrated in a vacuum. The resulting

residue is dissolved in methanol, mixed with a sodium methylate solution in methanol (29.7%, 50 ml) and is stirred for 12 hours. The clear solution is acidified with concentrated hydrochloric acid, brought to room temperature, diluted with water (200 ml). The resulting precipitate is suction filtered, washed with water and dried. Yield: 10.69g (95.0%).

^{13}C-NMR ($CDCl_3$, 100 MHz): δ 142.1, 142.0, 132.8, 132.63, 132.58, 131.8, 129.9, 127.9, 127.4, 125.9, 118.4, 116.9, 40.0.

d) 2-chloro-3-(2,4-dichlorophenylthio)-4-methyl-sulphonylamino-benzosulphonamide



Chlorosulphonic acid (3.69 ml) is dissolved in methylene chloride (100 ml), cooled to 0°C and added dropwise to a solution of 3-chloro-2-(2,4-dichlorophenylthio)-N-methylsulphonyl-aniline (10.6g) in methylene chloride (100 ml). After an hour, phosphorus pentachloride (23.07g) is added and the mixture is stirred for one more hour at 0°C. Following this, the solution is brought to room temperature and stirred for a further one hour. The precipitate is suction-filtered and the filtrate is emptied onto an iced water mixture. The organic phase is separated, dried (Na_2SO_4), filtered and concentrated in a vacuum. The resulting residue is dissolved in dioxan (80 ml) and is added dropwise to a mixture of dioxan (80 ml) and concentrated aqueous ammonia (120 ml), cooled to 0°C. The resulting mixture is stirred for a further 2 hours at room temperature. Following this, it is diluted with water (250 ml),

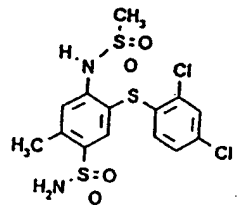
acidified with concentrated hydrochloric acid and cooled to room temperature. The resulting crystals are suction-filtered, washed with ethanol and dried in a vacuum. Yield: 6.74g (59.0%).

^{13}C-NMR (d_6-DMSO, 100 MHz): δ 145.5, 138.7, 133.5, 131.8, 131.1, 131.1, 129.3, 128.3, 127.5, 123.5, 120.4, 41.4.

The following compounds were prepared analogously to Example 1:

Example 2: 5-(2,4-dichlorophenylthio)-2-methyl-4-methylsulphonylamino-benzosulphonamide

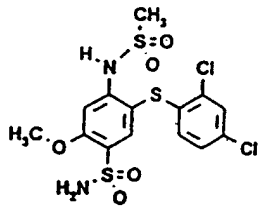
$C_{14}H_{14}Cl_2N_2O_4S_3$
FW: 441.38 gmol^{-1}



Mp: 250-253°C
^{13}C-NMR (d_6-DMSO, 100 MHz): δ 153.8, 138.2, 137.8, 137.3, 134.0, 130.1, 129.0, 128.6, 128.2, 127.0, 120.5, 113.2, 41.0, 20.8.

Example 3: 5-(2,4-dichlorophenylthio)-2-methoxy-4-methylsulphonylamino-benzosulphonamide

$C_{14}H_{14}Cl_2N_2O_5S_3$
FW: 457.38 gmol^{-1}



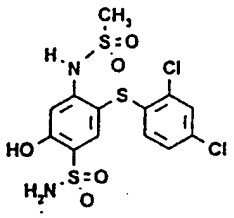
Mp: 258-262°C

^{13}C-NMR (d_6-DMSO, 100 MHz): δ 158.2, 145.2, 136.2, 135.4, 131.3, 131.1, 129.3, 128.8, 128.3, 11.3, 106.4, 56.6, 41.0.

Example 4: 5-(2,4-dichlorophenylthio)-2-hydroxy-4-vinylsulphonylamino-benzosulphonamide

$C_{13}H_{12}Cl_2N_2O_4S_3$

FW: 443.35 gmol^{-1}

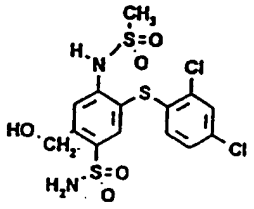


^{13}C-NMR (d_6-DMSO, 100 MHz): δ 157.6, 145.0, 137.0, 135.9, 130.9, 130.8, 129.2, 128.3, 128.0, 127.2, 109.6, 108.7, 56.2, 18.7.

Example 5: 5-(2,4-dichlorophenylthio)-2-hydroxymethyl-4-methylsulphonylamino-benzosulphonamide

$C_{14}H_{14}Cl_2N_2O_5S_3$

FW: 457.38 gmol^{-1}



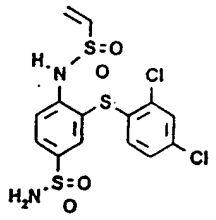
Mp: 185-187°C

^{13}C-NMR (d_6-DMSO, 100 MHz): δ 138.0, 136.6, 135.5, 134.3, 133.7, 133.2, 130.9, 129.5, 128.6, 128.3, 128.2, 127.2, 41.1, 34.3.

Example 6: 3-(2,4-dichlorophenylthio)-4-vinylsulphonyl-amino-benzosulphonamide

$C_{14}H_{12}Cl_2N_2O_4S_3$

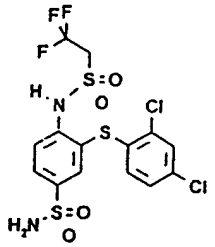
FW: 439.36 $gmol^{-1}$



Mp: 180-182°C

^{13}C-NMR (d_6-DMSO, 100 MHz): δ 132.2, 140.3, 136.7, 134.3, 132.9, 132.8, 130.8, 129.7, 128.6, 128.3, 127.8, 127.0, 125.5, 40.0.

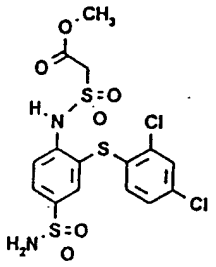
Example 7: 3-(2,4-dichlorophenylthio)-4-(2,2,2-trifluoro-ethyl)sulphonylamino-benzosulphonamide



Mp: 210-213°C

^{13}C-NMR (d_6-DMSO, 100 MHz): δ 143.0, 139.2, 134.7, 133.3, 133.0, 132.3, 130.1, 130.0, 129.8, 128.6, 127.1, 126.7, 123.7, 120.9, 55.45, 55.15, 54.85, 54.55.

Example 8: 3-(2,4-dichlorophenylthio)-4-methoxy-carbonylmethylsulphonylamino-benzosulphonamide



Mp: 182-185°C

^{13}C-NMR (d_6-DMSO, 100 MHz): δ 163.5, 142.4, 140.3, 134.3, 132.9, 132.8, 132.4, 130.8, 129.7, 128.6, 127.1, 125.8, 57.5, 52.8.

EXAMPLE A

Human COX-2 Test

Cells of a human monocytoid cell line were stimulated with lipopolysaccharide (LPS) (incubator at 37°C, 5% CO_2-enriched atmosphere and almost 100% atmospheric humidity), in order to induce COX-2. Following this, the culture medium (RPMI 1640, enriched with 10% FCS, 2 mM glutamine, 10000 U/ml penicillin, 10 ng/ml streptomycin and 1 mM pyruvate) is refreshed and potential inhibitor substances of cyclooxygenase-II, dissolved in culture medium or in phosphate-buffered saline or in some other solvent compatible with cell cultures, are added and then incubated for half an hour as described above. Arachidonic acid is added by pipette and incubation is carried out for a further 15 minutes. The culture supernatant of the cells is removed and its content of products of cyclooxygenase metabolism (e.g. Prostaglandin E2, Prostaglandin F_{1a}, Thromboxane B_2) is measured by ELISA.

EXAMPLE B

Human COX-1 Test

Inhibition of the arachidonic acid-induced aggregation of washed human thrombocytes was used as a test system for an estimation of the inhibition of cyclooxygenase-I. A thrombocyte suspension at 37°C was added to the test substances 2 minutes before addition of the arachidonic acid (10 μM final concentration) and the aggregation course was recorded via an aggregometer. With the assistance of a concentration-effect curve, the concentration of test substance was determined at which 50% aggregation was measured (IC50).

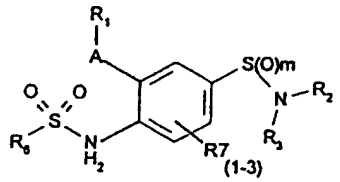
The results of both tests, and also the selectivity determined from the tests, are given in Table 1.

Table 1

Compound according to Example	COX I IC50 μM	COX II IC50 μM	COX I/COX II
1	25	0.10	250
6	20	0.10	200

Claims

1. Compounds of formula I



wherein
A denotes oxygen, sulphur or NH,
R_1 denotes an optionally unsaturated alkyl or alkyloxyalkyl group, optionally mono- or polysubstituted or mixed substituted by halogen, alkoxy, oxo or cyano, a cycloalkyl, aryl or heteroaryl group optionally mono- or polysubstituted or mixed substituted by halogen, alkyl, CF_3, cyano or alkoxy,
R_2 and R_3, independently from one another, denote hydrogen, an optionally polyfluorised alkyl group, an aralkyl, aryl or heteroaryl group or a group $(CH_2)_n$-X, or
R_2 and R_3, together with the N- atom denotes a 3- to 7-membered, saturated, partially or completely unsaturated heterocycle with one or more heteroatoms N, O or S, which may optionally be substituted by oxo, an alkyl, alkylaryl or aryl group, or a group $(CH_2)_n$-X,
X denotes halogen, NO_2, $-OR_4$, $-COR_4$, $-CO_2R_4$, $-OCO_2R_4$, $-CN$, $-CONR_4OR_5$, $-CONR_4R_5$, $-SR_4$, $-S(O)R_4$, $-S(O)_2R_4$, $-NR_4R_5$, $-NHC(O)R_4$, $-NHS(O)_2R_4$,
n is a whole number from 0 to 6,
R_6 denotes a straight-chained or branched alkyl group with 1-10 C-atoms, a cycloalkyl group, an alkylcarboxyl group, an aryl group, aralkyl group, a heteroaryl or heteroaralkyl group, which may optionally be substituted by halogen or alkoxy,
R_7 denotes halogen, hydroxy, a straight-chained or branched alkyl, alkoxy, acyloxy or alkyloxycarbonyl

group with 1-6 C-atoms, which may optionally be mono- or polysubstituted by halogen, $-NO_2$, $-OR_4$, $-COR_4$, $-CO_2R_4$, $-OCO_2R_4$, -CN, $-CONR_4OR_5$, $-CONR_4R_5$, $-SR_4$, $-S(O)R_4$, $-S(O)_2R_4$, $-NR_4R_5$, $-NHC(O)R_4$, $-NHS(O)_2R_4$, or a polyfluoroalkyl group,
R_4 and R_5, independently from one another, denote hydrogen, alkyl, aralkyl or aryl, and
m is a whole number from 0 to 2,
and the pharmaceutically-acceptable salts thereof.

2. Compounds of formula I according to claim 1, wherein R_7 denotes halogen, hydroxy or an alkyl or alkoxycarbonyl group with 1-4 C-atoms which may optionally be substituted by halogen or hydroxy.

3. Compounds of formula I according to one of claims 1 or 2, wherein R_1 may optionally be an unsaturated alkyl or alkyloxyalkyl group which may optionally be mono- or polysubstituted or mixed substituted by halogen, alkoxy, oxo or cyano.

4. A pharmaceutical composition containing as an active ingredient at least one compound of general formula I according to claim 1.

5. The use of compounds of formula I according to claim 1 as a means of treatment and alleviation of diseases or disorders which can be healed or alleviated by inhibition of the enzyme cyclooxygenase II.

6. The use of compounds of formula I according to claim 1 as a means for treatment or alleviation of inflammatory processes.

7. The use of compounds of formula I according to claim 1 as a means for treatment of pain.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB 98/00342

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C311/39 A61K31/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	DE 195 33 644 A (NYCOMED ARZNEIMITTEL GMBH) 13 March 1997 see the whole document ---	1-7
P,X	WO 97 03953 A (HAFSLUND NYCOMED PHARMA ;BLASCHKE HEINZ (AT); KREMMINGER PETER (AT) 6 February 1997 see the whole document ---	1-7
A	WO 94 13635 A (MERCK FROSST CANADA INC ;FORD HUTCHINSON ANTHONY W (CA); KENNEDY B) 23 June 1994 cited in the application -----	1-7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
20 March 1998	09.04.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Janus, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern. ..ial application No.
PCT/GB 98/00342

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 5-7
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 5-7 can be regarded as relating to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/GB 98/00342

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 19533644 A	13-03-97	NONE	
WO 9703953 A	06-02-97	AU 6361096 A	18-02-97
WO 9413635 A	23-06-94	US 5604260 A	18-02-97
		AU 5621594 A	04-07-94
		CA 2151235 A	23-06-94
		EP 0673366 A	27-09-95
		JP 8504408 T	14-05-96